

### Remarks

This Amendment is made in connection with the filing of a file-wrapper-continuation application, the parent application to which had been finally rejected. This response is therefore intended to be responsive to the Office Action dated July 30, 1991 in the file of the parent application. In that Office Action, the claims of this application were rejected both for lack of enablement and over the prior art. Based on the changes to the claims made above and the comments made here, the applicants respectfully request the Examiner to again reconsider the merits of this patent application.

#### Rejection to Claim 18 under §112

This rejection has been addressed by making the sequence recitation in claim 18 cover only identical sequences. This change should remove this particular ground of rejection.

#### First Rejection under §112 for Lack of Enablement

The Examiner, in the Office Action, rejected all the claims in the parent patent application on the grounds that the specification of this application is not enabling. This rejection is simply not appropriate.

The Examiner is both applying a tortured reading to the facts set forth in the specification and applying an incorrect legal standard. The facts do demonstrate that the applicants invention works better than the prior art, but even if the facts did not support his conclusion, that would not make the specification non-enabling.

The Examiner continues to argue that the applicants have not demonstrated with sufficient certainty that the synthetic genes described here kill insects better than the native genes. Even if this were true, that would not make the specification non-enabling. To meet the requirements of §112, first paragraph, the specification must teach how to use the invention. The specification here teaches a method of making altered nucleotide sequences and the specification contains a table of preferred codon usage for use in such sequences, and provides instructions and guidance on how to construct a synthetic sequence from the information on

the table. The Examiner does not dispute that, but asserts the specification is non-enabling by arguing that the evidence is not persuasive that the applicants' synthetic sequences are better than the prior art native sequences. This argument is misplaced, since it is legally irrelevant to the enablement question. It is nowhere a requirement of patentability, and certainly no a requirement of §112, that an invention be better. To be patentable, an invention must be new, useful and nonobvious, but not necessarily better. If the invention is an improvement, as this one truly is, that extent of the improvement goes to the obviousness question, but it is certainly not relevant to enablement.

Nevertheless, the facts do establish that the invention of the applicants is an improvement over the prior art. These synthetic sequences do express the B.t. toxins at higher levels than the native sequences. The Examiner continues to compare the wrong numbers. In analyzing the data from Table 1, the Examiner continues to look at the total number of plants tested versus the numbers which were highly rated killers. This is the wrong comparison. As explained in the specification, page 19, lines 11-36, the percentage of plants which killed insects at some level did not differ between the native sequence and the synthetic sequence. The lack of any significant expression of the inserted genes in random plants is a normal phenomenon in making transgenic plants and appears to be due to effects such as natural recombinations and site specific effects related to the locus of gene insertion, which is random. However, for those plants which did express, as indicated by the "Total Killers" column on the table, the percentage of highly rated killers was significantly better for the synthetic sequences as compared to the native sequence. Only two of the native sequence plants were rated 9, or only 10%, and a full 20% were rated 6. By contrast, all expressing plants with the synthetic sequences were rated 8 or 9, and a full half were rated 9. The applicants do not claim that the synthetic sequences increase the frequency of recovering expressing plants, they contend only that plants which do express tend to express at higher levels. The data presented in the specification clearly supports this interpretation.

The Examiner continues to be bothered by the fact that the exact criteria used for rating plants 6 through 9 were not set forth in detail in the specification. The applicants continue so insist that this does not make the

specification non-enabling of the invention. While it happens that the applicants' rating system was not subjective, even if it was subjective, there is no rule of law known to the applicants which makes subjective data irrelevant in determining enablement. Instead, the applicants' rating system was, as indicated in the specification, a series of ratings based on how long the insects lived and fed, before the insects ceased feeding and died. The ratings were simply differences in length of survival and were interpolated, as mentioned in the specification, between a survival of several days (rating 5) and virtual immediate cessation of feeding (rating 9). The exact times used in this rating system is not at all necessary to practice this invention. The rating systems used was arbitrary, and any number of similar tests can be designed by anyone skilled in this art. The point of the test was only to demonstrate that the synthetic sequences expressed better than the native sequences. Since they do that, and since the specification enables construction of many such synthetic sequences, the specification is fully enabling and this rejection is improper.

#### Second Rejection under §112 for Lack of Enablement

For the purpose of trying to find patentable subject matter in this application, the applications have now limited all the claims in the application to B.t. genes which kill Manduca sexta. This is done without prejudice to re-instituting similar claims later, and was done to remove this ground of rejection so as to narrow the issues for any further prosecution or appeal.

#### Third Rejection under §112 for Lack of Enablement

This rejection asserts that the claims should be limited to the specific sequences recited in the drawings. The applicants assert that the specification is clearly enabling for recognized variations of Lepidopteran-specific B.t. toxin genes. As discussed in the specification (page 2, lines 25-36), there are several related B.t. genes which are relatively highly homologous at the amino acid level. The particular genes with this high homology to the sequence presented in the application are the genes which have Lepidopteran specific toxicity. Since the present claims are recited toxicity to Manduca sexta, all the claims now read on such Lepidopteran specific B.t. genes. Clearly it is logical to expect these very sequence similar

and functionally similar genes to have similar expression characteristics. The Examiner has advance no reason why the other B.t. gene would not be affected similarly other than a general allegation of unpredictability. The Examiner assert that there is inherent unpredictability in the expression of foreign genes. The applicants do not completely agree. The various B.t. toxin genes can all be expressed in truncated form in plants, and they all express relatively poorly in plants compared to other genes which have been expressed in plants. The poor level of gene expression is characteristic of these particular genes and it is this poor is the level of gene expression which the present invention is intended to change. The fact that there is some variability does not make the practice of the invention wholly unpredictable. The scope of the present claims are clearly well within the expected variation in this invention which is to be expected to work, once the Examiner accepts the fact that the synthetic gene sequences do work better.

#### Rejection under §103 over Prior Art

The Examiner also continues to reject the claims of the present application over a combination of seven prior art references. The primary reference, to Hoekema, discloses research done in yeast establishing that a specific gene in that organism which expresses well can be made to express poorly if its pattern of codon usage is altered. From that observation, and the acknowledged fact that the B.t. genes were difficult to express well in plants, the Examiner has found all the applicants' claims to be obvious. Of course, the applicants respectfully disagree.

First, it is still true that no reference is cited which shows taking a gene which expresses poorly and changing only the codon usage to achieve better expression. Yet that is what the applicants here have done. The applicants still assert that Hoekema's observation that a highly expressed gene can be altered to express less efficiently does not assure that a poorly expressed gene can be made to express better.

It is also still true that the work of Hoekema in yeast cannot be directly transferred into plants. Plants and yeast are simply not that closely related. Note that Hoekema recited that changing up to 22 rare codons at the 5' end of the gene had very little effect on the expression level. Hoekema only noted any significant change in expression level when over 64 codons, representing 15% of the codons in the coding region, were changed. By

contrast, in plants the applicants here were able to obtain increased expression of the synthetic gene by only changing 59 codons at the 5' end of the gene, representing less than 10% of the codons in the whole protein. Also, the Hoekema paper notes that the yeast gene which he investigated uses in excess of 96% preferred yeast codons in its native state, while no known plant genes are that constrained in their codons usage. Yet the applicants were able to obtain increased expression by converting only 10-25% of the codons to a preferred codon choice. Thus, it is clear that the lessons from yeast can not be directly transferred to plant systems. All that Hoekema suggests is a reasonable avenue for inquiry, not a reasonable certainty that successful results could be obtained.

It is further worthy of note that enhanced production of the B.t. gene in plants is a highly sought-after result. The ability to make insect-resistant plants was one of the early high-profile promises of plant biotechnology. As such, many groups have worked on this problem and this toxin has proven unusually difficult to express well in plants. Given this fact, and given the lack of clear understanding of the causes of the difficulty in expressing B.t. genes in plants, these references only suggest an invitation to experiment by trying codon substitution, not a suggestion of a desirable outcome. As such, the references do not make this claimed invention obvious.

In the Office Action, the Examiner has asserted that the present claims are not limited to the use or avoidance of any specific codons. This is wrong. While specific codons are not recited in the claims, limitations are in the claims which make it clear where "preferred" codons are recited, and the definition of such preference in the specification makes it clear how one determines which codons are preferred and which are not. Thus the claim language does exclude the non-preferred codons from the critical regions of the claimed sequences.

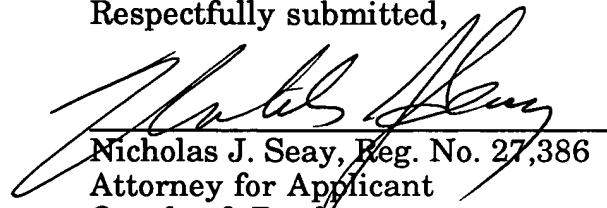
Also, the Examiner's assert that one of the modified sequences did not work as well as the controls is wrong. Again, the Examiner is comparing the wrong numbers. Although, by chance, many of the plants transformed with pTVAMVBT4 do not express the toxin at any level (which does happen at some frequency with any gene inserted in this manner) all the pTVAMVBT4 plants which did expressed expressed at

high levels, being rated 8 or 9. Thus the Examiners attack on the applicant's arguments are based on faulty reasoning.

Conclusion

Wherefore, again the Examiner is respectfully requested to revisit the merits of the specification and claims of this patent application. An early and favorable reply is solicited. A separate request for extension of time has been submitted under separate cover in the parent application so that this FWC continuation application will be co-pending therewith.

Respectfully submitted,



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